MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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Update on the Treatment of Uveal Melanoma

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H&O How common is uveal melanoma, including metastatic uveal melanoma?

RC Uveal melanoma is rare, with an incidence of approximately 5 cases per million people in the United States—which makes approximately 1500 cases a year. Most patients present with primary disease, although a small minority of patients present with metastatic disease at diagnosis.

H&O What are the signs and symptoms?

RC Patients often present with visual changes, although some patients have no symptoms and are diagnosed by their ophthalmologist or optometrist on routine eye exam. Unlike most malignancies, the diagnosis of uveal melanoma can be made based on physical examination and is not dependent on biopsy results.

H&O In what ways is uveal melanoma different from other forms of melanoma?

RC Uveal melanoma arises from melanocytes, just like cutaneous melanoma, but the etiology is different. For example, uveal melanoma seems to have a very low genetic mutational burden, whereas cutaneous melanoma has a very high mutational burden. Cutaneous melanoma exhibits *BRAF* mutations in 45% of cases and *NRAS* mutations in 15% to 20% of cases, but we rarely if ever see these mutations in uveal melanoma—the incidence is less than 1%.

The most frequent mutations we see in uveal melanoma are those in *GNAQ* and *GNA11*. Activation of the GNAQ and GNA11 proteins leads to activation of the mitogen-activated protein kinase (MAPK) pathway, the protein kinase C (PKC) pathway, the phosphoinositide 3-kinase (PI3K)/AKT pathway, the Hippo-YAP pathway, and others. The *GNAQ* and *GNA11* mutations in uveal melanoma can be seen as analogous to the *RAS* mutations we find in cutaneous melanoma, which also activate the MAPK pathway.

Other recurring genetic alterations that occur in uveal melanoma include loss of the tumor suppressor gene *BAP1*, mutations in the splice factor *SF3B1*, and mutations in *EIFAX*. More recently, mutations in cysteinyl leukotriene receptor 2 (*CYSLTR2*) and *PCLB4* have been found in uveal melanoma.

H&O What is the general approach to treatment?

RC Treatment involves either surgery or radiotherapy. Surgery usually consists of removal of the entire eye. Radiotherapy sometimes involves proton-beam therapy or heavy-particle radiation, but most patients in the United States receive plaque brachytherapy. In plaque brachytherapy, a pouch filled with radioactive pellets is sewn into the eye, where it generally remains for 3 days. In a 2004 publication, the Collaborative Ocular Melanoma Study Group found that survival outcomes in primary disease were the same for plaque brachytherapy as for surgical enucleation.

Although these treatments offer excellent local

control of disease, approximately half of patients develop recurrent disease and metastasis. Late recurrences—taking place 10, 15, or 20 years after initial treatment—are more common with uveal melanoma than with other cancers.

H&O How do physicians determine which patients are at the greatest risk for recurrence?

RC We can use tumor, node, metastasis (TNM) stage, cytogenetics, and gene expression profiling to determine who is at the greatest risk for recurrence. Fine-needle aspirate at the time of plaque brachytherapy is used to detect monosomy 3p or gains of chromosome 8q, which suggest an increased risk of recurrence.

There is also a commercial assay available that looks at the tumor's gene expression profile to determine which patients are at elevated risk for recurrence. The assay divides tumors into class 1a, 1b, and 2. Class 1 tumors are the good actors, with a 5% to 10% risk of recurrence. Class 2 tumors are the bad actors, whose median time to recurrence is on the order of 30 to 36 months. Tumors that fall into class 1 are more likely to have *SF3B1* mutations.

H&O What is the treatment approach for patients with metastatic uveal melanoma?

RC There is no standard therapy for patients with recurrent disease. The first decision is whether to use systemic therapy or regional therapy. The majority of recurrences occur in the liver, so some physicians will initially focus on liver-directed therapies, which may include bland embolization, radioembolization, chemoembolization, intrahepatic chemotherapy, and other treatment modalities. All of these therapies have modest response rates and durations of disease control, although there is no conclusive evidence that they work better than systemic therapy.

Regarding systemic therapy, the treatments that we use for cutaneous melanoma do not work well in uveal melanoma. Chemotherapy works poorly in cutaneous melanoma and even worse in uveal melanoma, and targeted therapies such as vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) or dabrafenib (Tafinlar, Novartis) do not apply because *BRAF* mutations are not a characteristic of uveal melanoma. Results with checkpoint inhibitors in uveal melanoma also have been disappointing. A study that Dr Katy Tsai presented at the 2016 American Society of Clinical Oncology (ASCO) annual meeting in which researchers identified 58 patients with uveal melanoma who had received pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), or atezolizumab (Tecentriq, Genentech) found that durable responses to checkpoint inhibitors were rare.

H&O What other approaches to treatment are being studied?

RC A major line of research has been focused on inhibition of the MAPK pathway. We undertook a phase 2 trial through the Cancer Therapy Evaluation Program (CTEP) in which we randomly assigned patients to either the experimental MEK inhibitor selumetinib or chemotherapy. In our trial, we had a response rate of 14% with selumetinib vs 0% with chemotherapy. We also were able to double progression-free survival from approximately 2 months with chemotherapy to 4 months with selumetinib. We published these results in the *Journal of the American Medical Association* in 2014.

Based on these encouraging results, AstraZeneca funded a pivotal registration trial called SUMIT (Selumetinib in Metastatic Uveal Melanoma). This is a large, international trial in which we decided to look at selumetinib/dacarbazine vs placebo/dacarbazine, rather than selumetinib alone vs dacarbazine alone.

As we reported at the 2015 annual meeting of the Society for Melanoma Research (SMR), we found no significant difference in progression-free survival or response rate between the 2 arms. The different outcomes observed in the phase 2 vs phase 3 randomized trials of selumetinib in uveal melanoma may be partially attributable to differences in patient population as well as in the study design.

H&O Have there been any advances in uveal melanoma in the past few years?

RC Yes, we are seeing far more research in the field of uveal melanoma, and research funding has increased. When I began specializing in this area 10 years ago, there was much less going on in the field than there is now. Clinical trials are currently looking at targeting the PKC and MAPK pathways, either alone or in combination with other therapies. We already have some evidence that the inhibition of multiple pathways can improve outcomes in uveal melanoma.

We still do not fully understand the potential therapeutic role of MEK inhibition in uveal melanoma. For example, it is not clear whether we are dosing all of our oral inhibitors correctly. Data from our phase 2 trial of selumetinib suggest that greater inhibition of MEK is associated with a greater clinical response, but MEK inhibition also produces dose-dependent toxicities. Thus, it may be that intermittent dosing might work better than continuous administration by allowing us to administer higher doses, achieve greater target inhibition, and prevent feedback activation that may limit treatment efficacy. We will soon be initiating a phase 1 trial that will examine increasing doses of intermittent selumetinib.

H&O What other important research in uveal melanoma has come out recently?

RC Results from a study with AEB071, a PKC inhibitor from Novartis, were presented by Dr Sophie Piperno-Neumann at the 2014 ASCO annual meeting. Novartis also is developing a next-generation PKC inhibitor that may be better tolerated than the first-generation agent.

In addition, Immunocore is developing a bispecific molecule called INC gp100 that targets the glycoprotein 100 melanocyte antigen and brings CD3-positive T cells adjacent to the tumor cells. The initial phase 1 study of this agent included a number of patients with uveal melanoma and produced promising preliminary data; Dr Sophie Piperno-Neumann presented results from this trial at the 2014 annual meeting of the SMR. A second phase 1 trial of this agent using a different dosing schedule in patients with uveal melanoma is currently accruing patients (NCT02570308). In addition, a pivotal trial is being developed for this disease.

There is an unmet need for therapy to reduce the risk of recurrence, so we are studying the use of adjuvant therapy in patients who are at high risk for recurrence. Our group at Columbia University is testing the use of crizotinib (Xalkori, Pfizer) as an inhibitor of c-MET (NCT02223819) in patients with high-risk uveal melanoma after treatment of the primary lesion, based on preclinical research from Oliver Surriga in the laboratory of Dr Gary K. Schwartz here at Columbia University Medical Center.

Dr Takami Sato at Thomas Jefferson University is leading an ongoing phase 2 trial that is examining the use of sunitinib (Sutent, Pfizer) vs valproic acid in patients with high-risk uveal melanoma (NCT02068586).

H&O What do you think the focus of future research should be?

RC The key is to better understand the biology of uveal melanoma. For example, what allows for the long latency period before recurrence? This is a disease that seems as if it should be simple to understand and treat because it is so simple genetically. Other factors are at work, however, including epigenetic alterations, so understanding the epigenetic changes that are driving this disease is very important.

Suggested Readings

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